
GenieUs
GenieUs Genomics
Genetics in ALS
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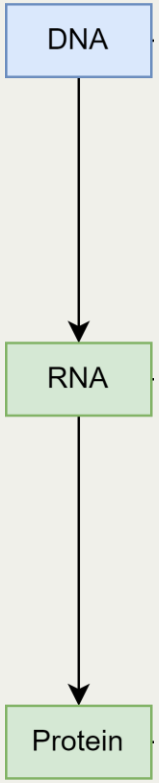
Contents

Background

Background



The central dogma of biology

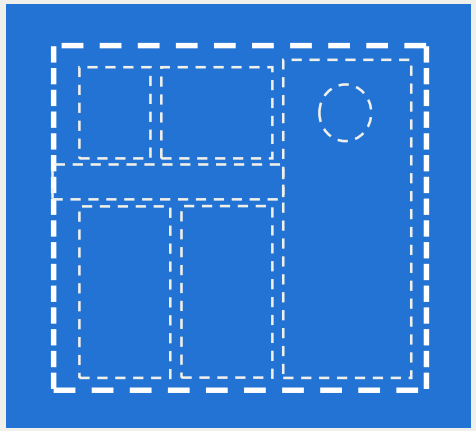
“DNA, makes RNA, makes protein”

Background

Textbook

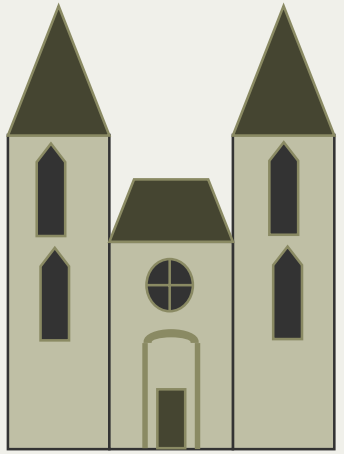
DNA

Blueprint



RNA

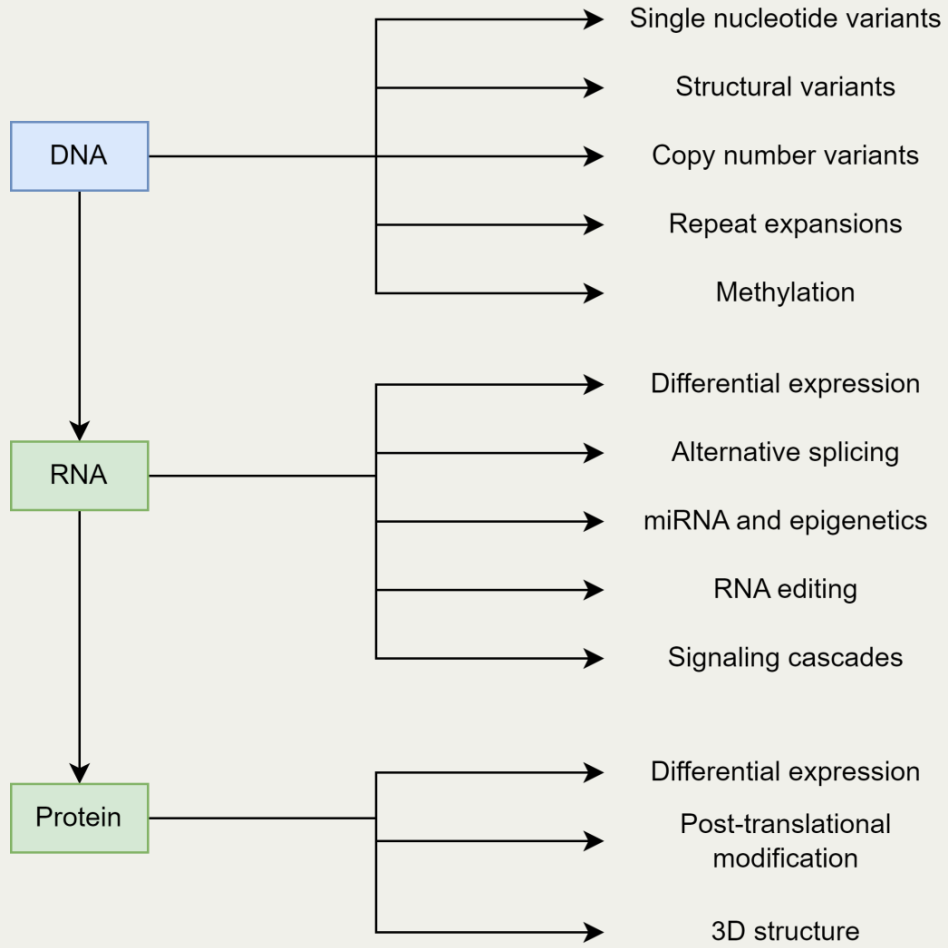
Building



Protein

Background

The central dogma of biology



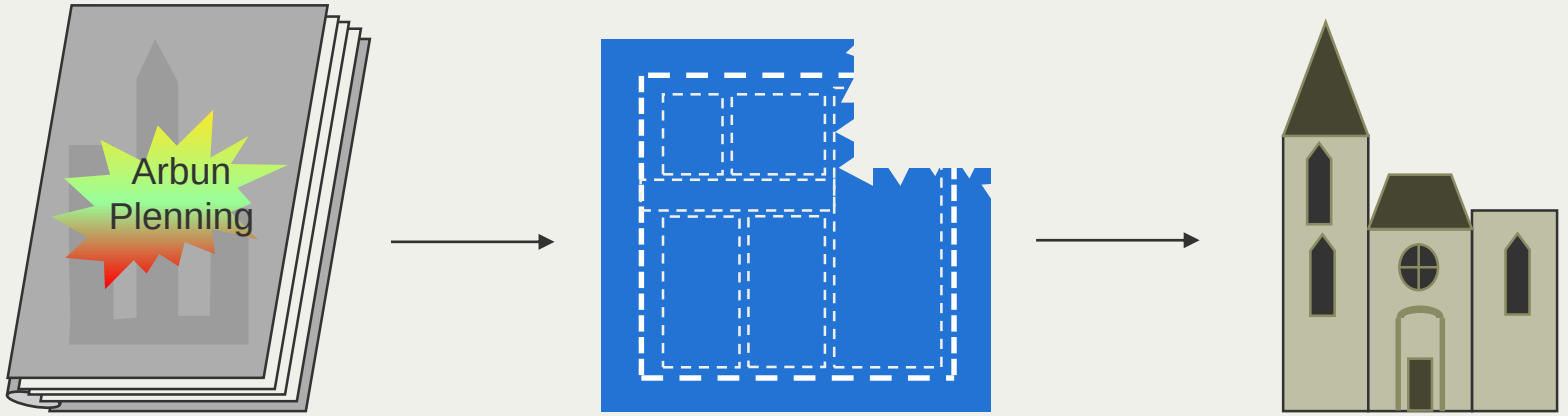
The reality of biology

Any one of these variant types could drive disease.

Multiple variants might contribute to disease.

We need to look at as many levels as possible to understand complex diseases.

What do genetic variants do?



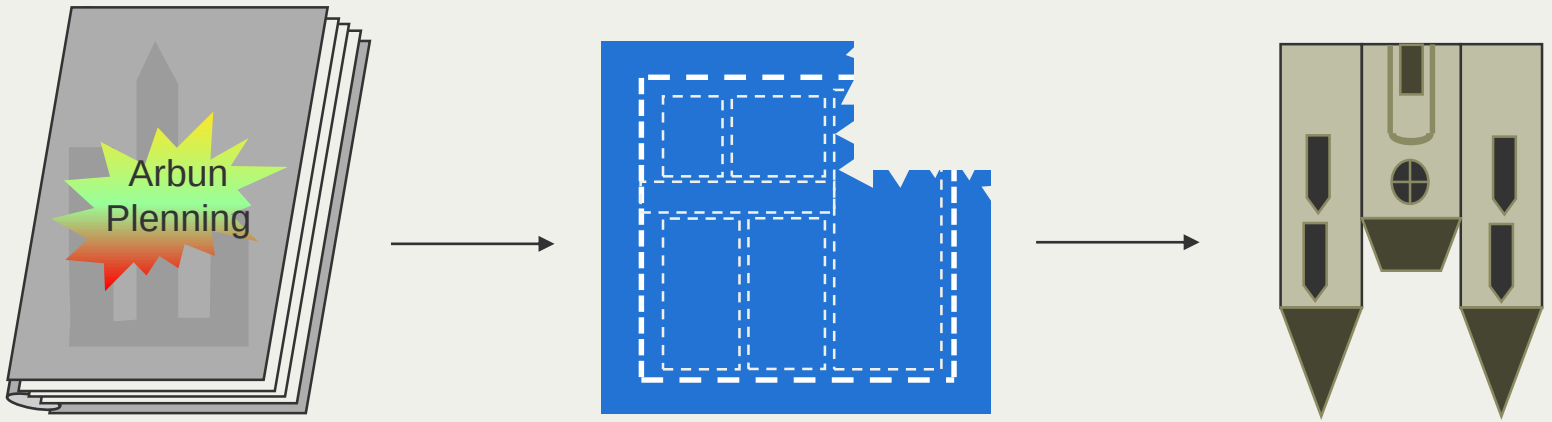
DNA → RNA → Protein

Consequenc
e

The building isn't finished.

The protein is missing something important.

What do genetic variants do?



DNA → RNA → Protein

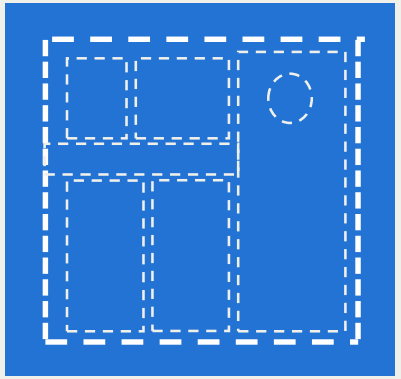
Consequenc
e

The building is impossible!

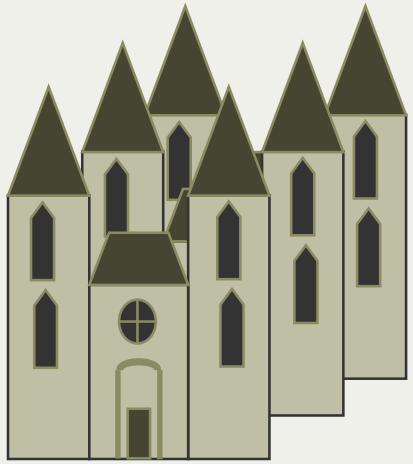
The protein cannot be made.

What do genetic variants do?

DNA



RNA



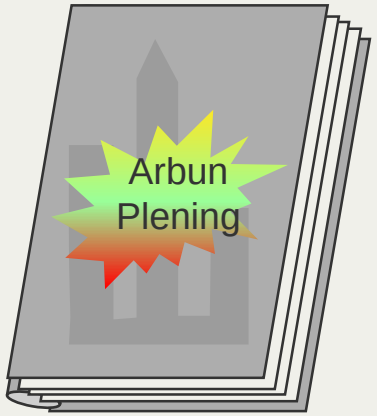
Protein

Consequenc
e

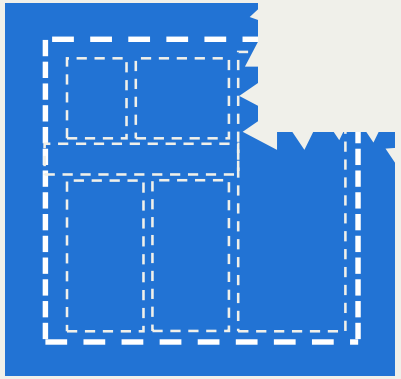
It’s done, but we only needed one!

The wrong amount of protein was made.

What do genetic variants do?



DNA



RNA

Protein

Consequenc
e

The building is on fire!

The protein doesn’t work and it damages nearby structures as well.

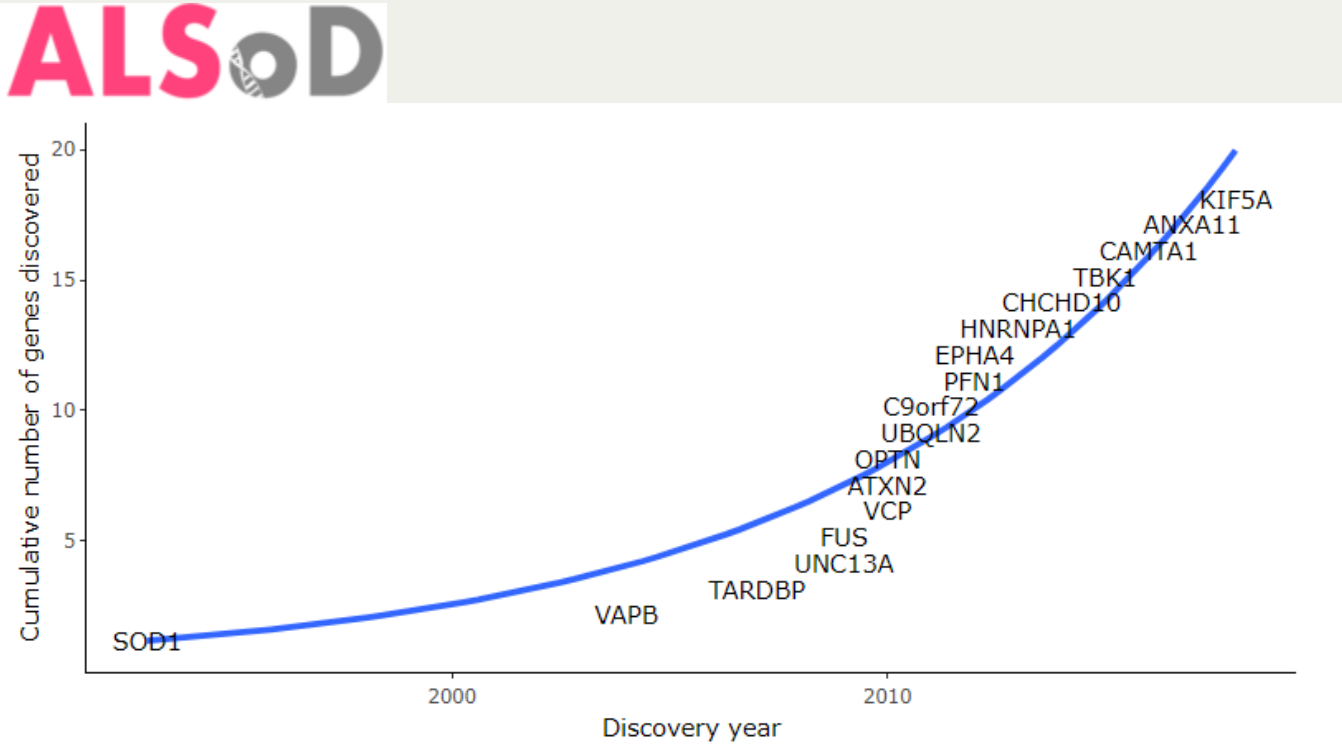
Genetic Biomarkers in ALS

What is a biomarker?

Diagnostic - A naturally occurring molecule, gene or characteristic by which a particular pathological process can be identified.

Prognostic – A molecule, gene or characteristic with the ability to predict how rapidly a disease will progress, or what symptoms will emerge.

Genetic biomarkers in ALS



Monogenic causative variants

Many of the genes presented on this graph host variants that are **100% penetrant.**

This means that they cause ALS in everybody that has these variants.

These are **Diagnostic genetic biomarkers.**

Genetic biomarkers in ALS

Shortcomings of genetic biomarkers

Onset

There is no apparent uniform onset age or type for most causative variants in ALS.

Progression

Specific genetic variants don’t always provide information regarding which symptoms will emerge next.

ALS variants don’t always correlate with loss of function on the ALSFRS-R scale.

Clinical end point

Genetic variants offer limited insight regarding remaining patient lifespan.

Most ALS variants do not indicate whether a patient will respond to one type of therapy or another.

Genetic biomarkers in ALS

Shortcomings of genetic biomarkers

Meta-Analysis > J Neurol Neurosurg Psychiatry. 2010 Dec;81(12):1324-6.
doi: 10.1136/jnnp.2010.207464. Epub 2010 Sep 22.

An estimate of amyotrophic lateral sclerosis heritability using twin data

A Al-Chalabi [1], F Fang, M F Hanby, P N Leigh, C E Shaw, W Ye, F Rijsdijk

Missing heritability

Only 10 – 15% of ALS patients have fully penetrant causative variants.

We know however that there are genetic contributions in about 60% of ALS cases, so **the majority of disease driving variants remain to be discovered.**


Discovering genetic contributors to ALS

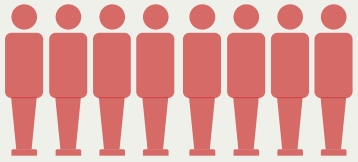
How did we get here?

GWAS

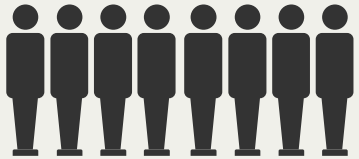
This stands for Genome Wide Association Study.

These studies identify genetic regions that contain variants that are more prevalent in ALS patients than controls. Successful GWAS requires thousands of patients.

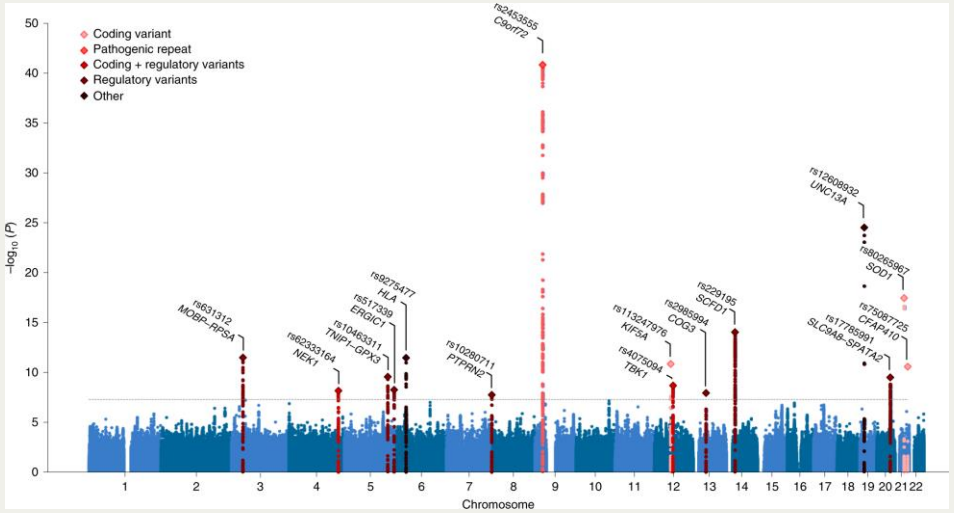
Variants identified by GWAS are only associated with disease and not necessarily causative. Sometimes variation in these regions contribute to disease severity rather can being the cause in themselves.



ALS patient group



Healthy control group



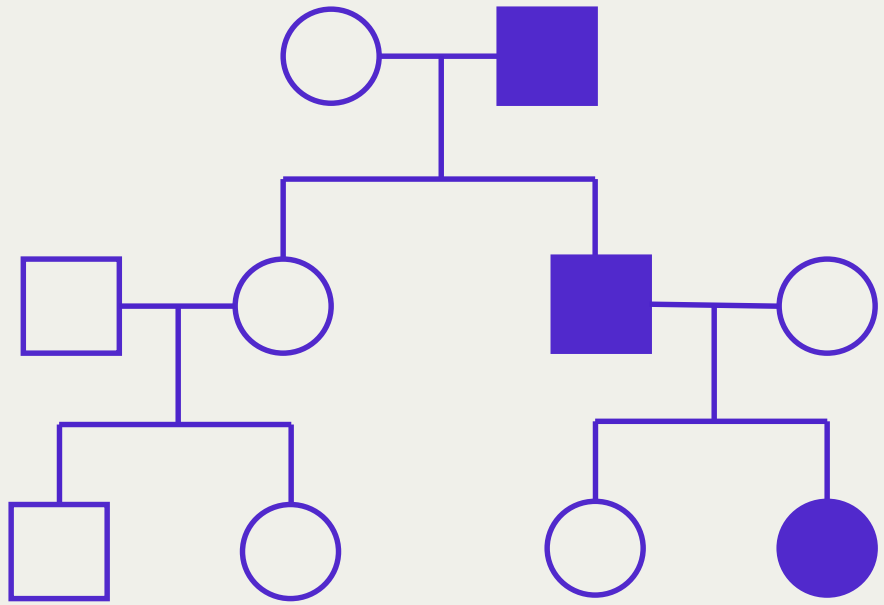
How did we get here?

Family pedigree

Obtaining genetic information from families with affected and unaffected individuals can be helpful to identify causative variants.

In this case, rare harmful variants will only be detected in symptomatic family members.

These variants can be unique to families or in some cases be found in other families by searching disease databases. It would also be expected that these variants don't occur in databases of non-affected individuals.



Affected male

Affected female

Unaffected male

Unaffected female

How can we go further with genetics?

Mechanistic understanding – Clinical modifiers

What are they?

Genetic variants that don’t necessarily cause ALS, but they do make it worse in people who already have the disease.

Why are they useful?

- They deepen our understanding of disease
- They may guide therapeutic decisions
- They may become therapeutic targets that benefit a subsection of the ALS population

Example – UNC13A

This gene hosts a number of variants that are pretty common in the general human population.

Two of these variants were associated with shorter survival time in ALS.

Patients with these variants respond positively to Lithium Carbonate treatment.

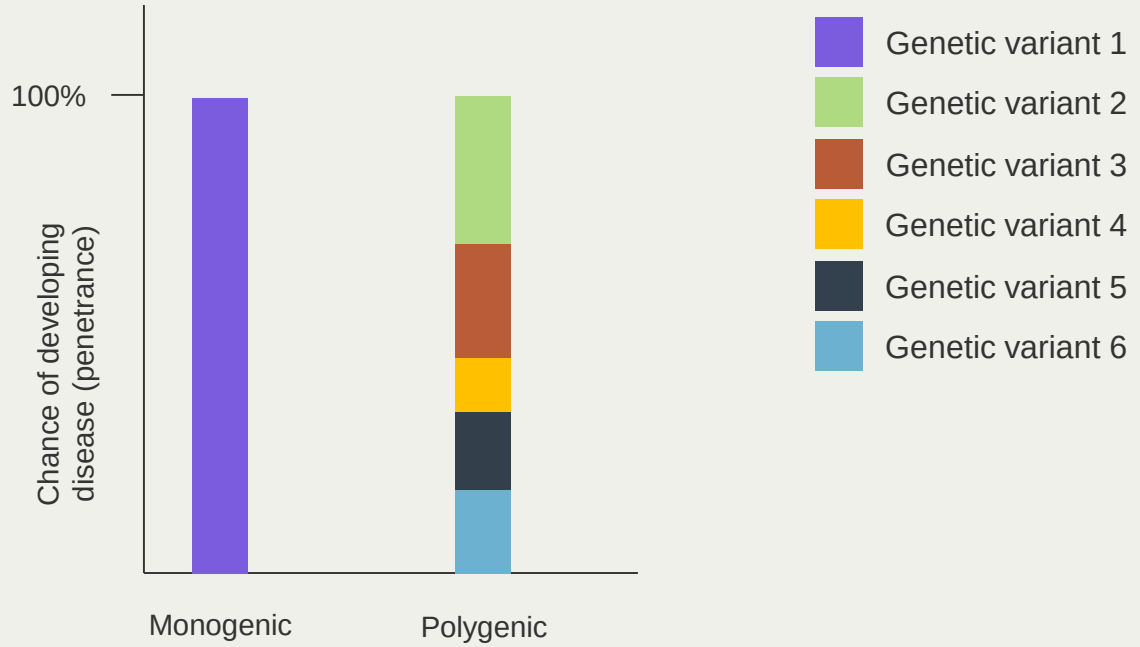
How can we go further with genetics?

Mechanistic understanding – polygenic disease

What are they?

So far we have talked about monogenic causes where one specific variant will cause the disease.

Polygenic diseases require multiple genetic variants for the disease to emerge.



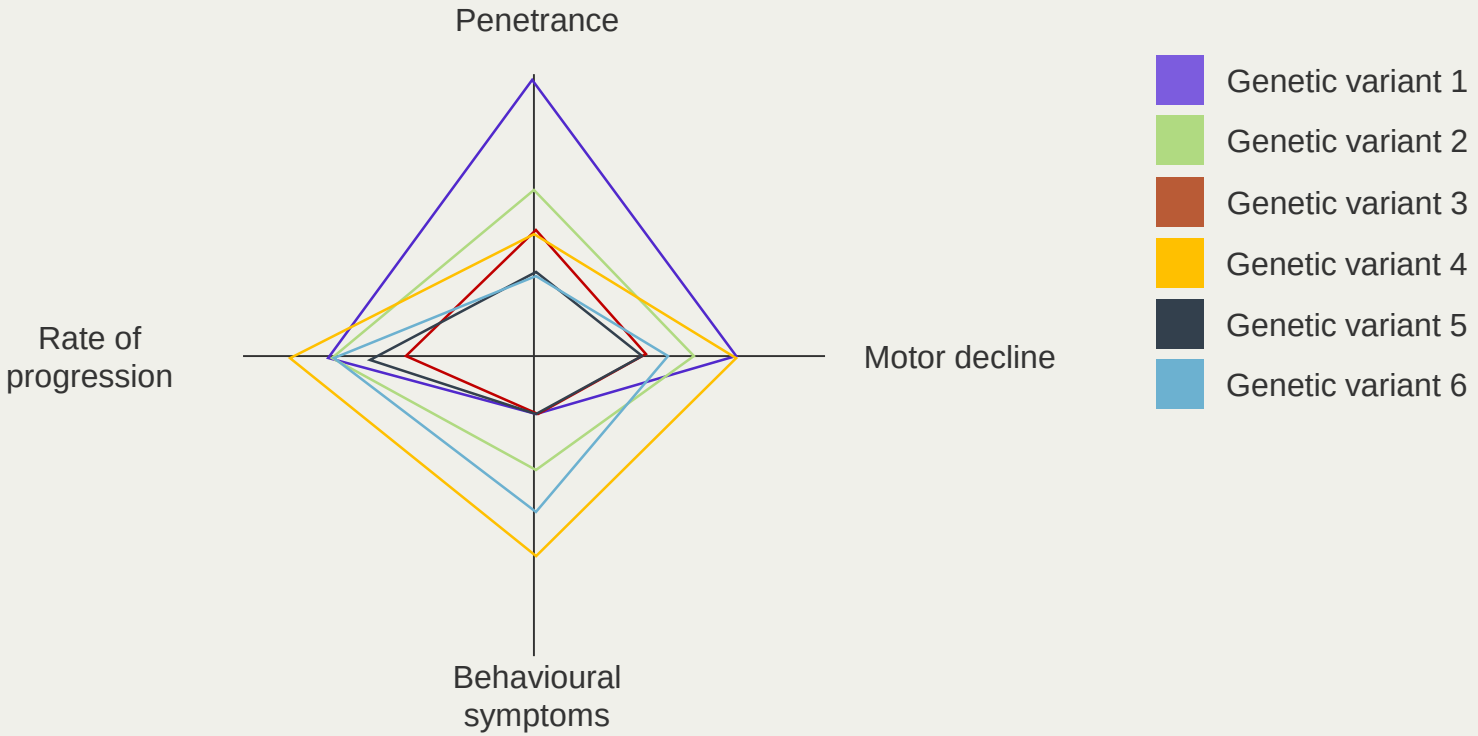
How can we go further with genetics?

Mechanistic understanding – polygenic disease and clinical modifiers

Integrated understanding

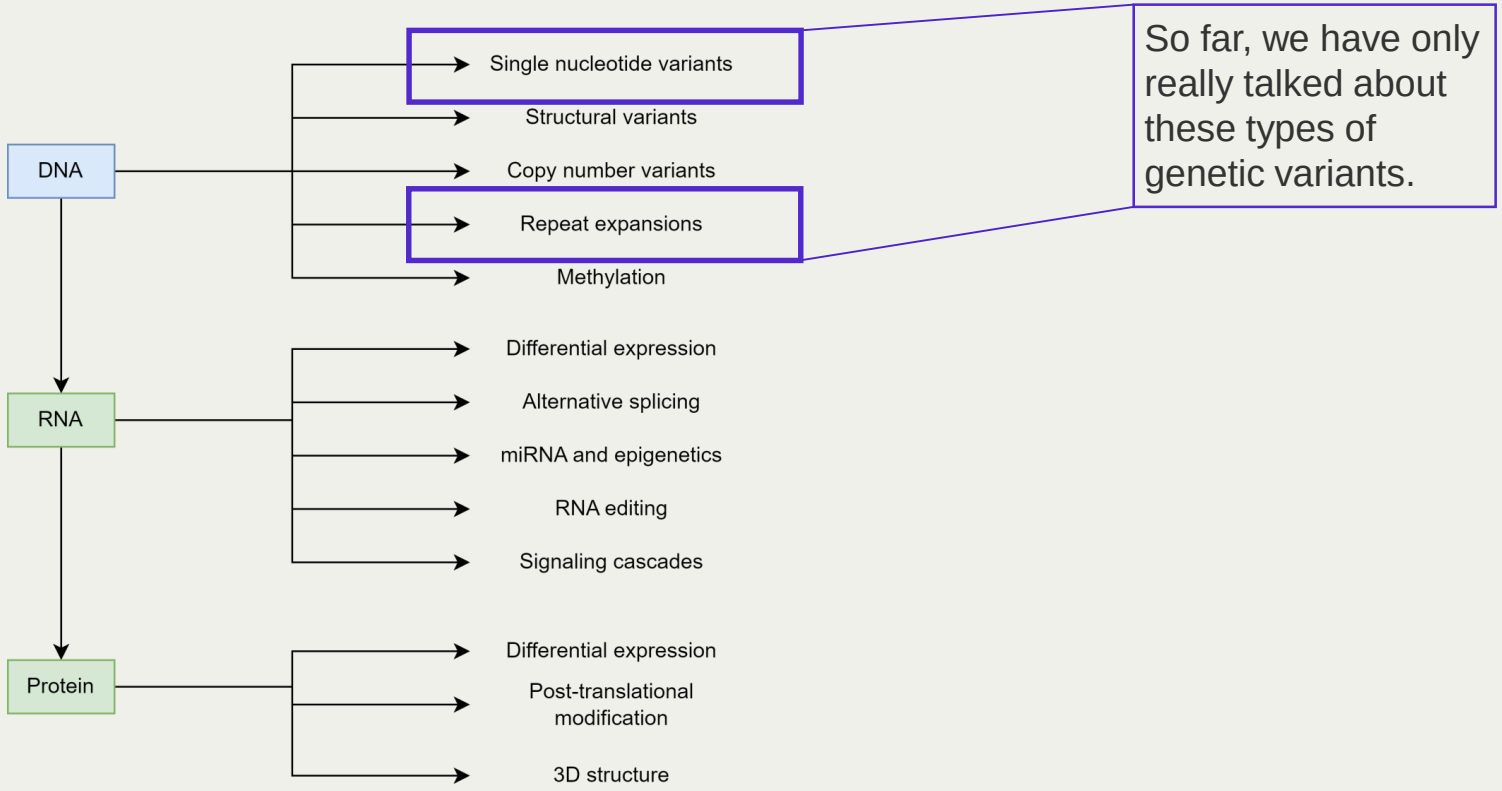
Assessment of multiple genetic features may be necessary to understand disease in individual patients.

An integrated perspective allows us to identify multiple **genetic drivers of disease**.



How can we go further with genetics?

Mechanistic understanding – multi-omic perspective



Disease coverage

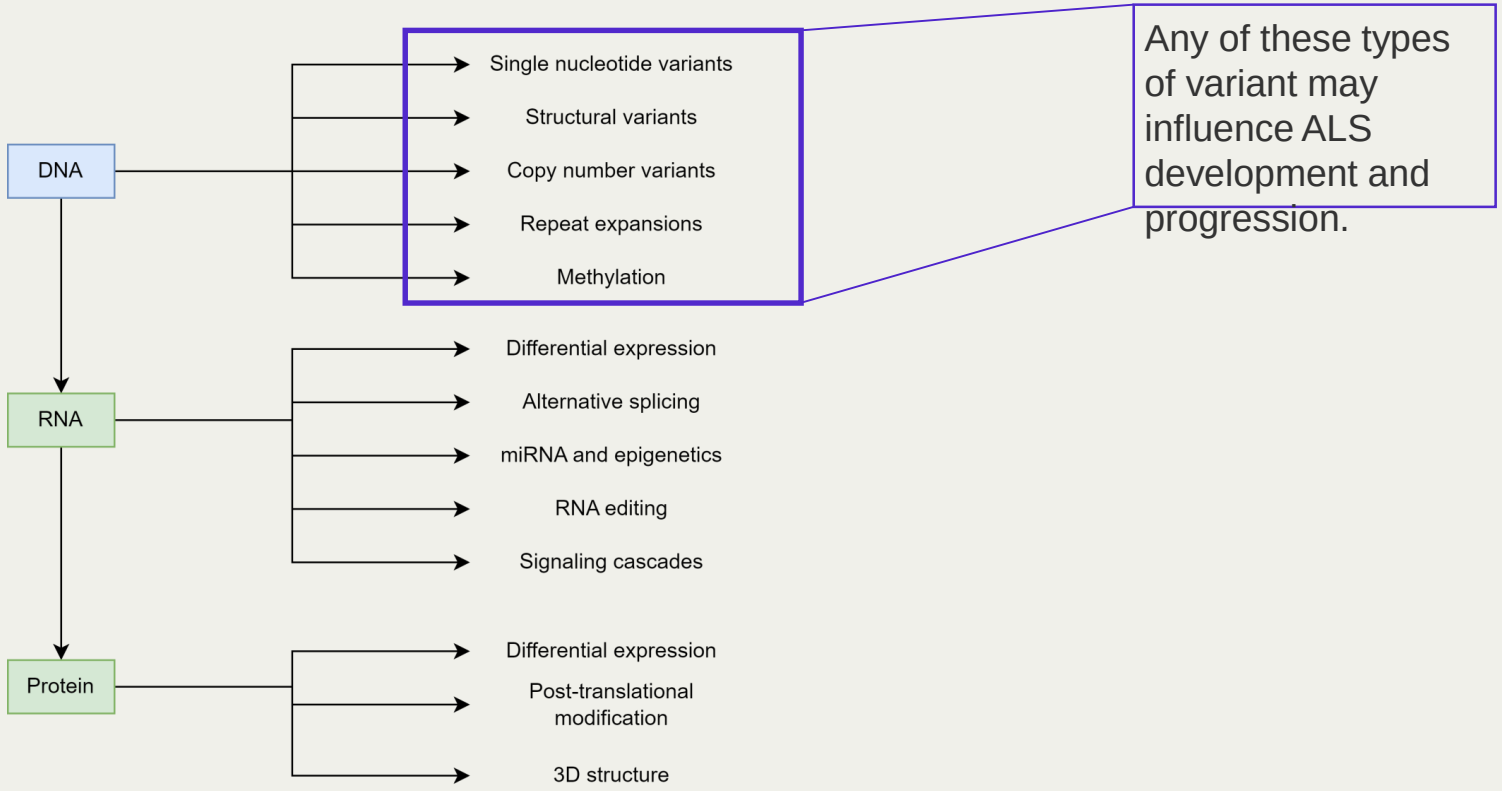
Almost all of the genetic variants we understand in ALS are single nucleotide variants or repeat expansions.

There are many types of genetic variation possible, and any of them (or all of them!) could have a role to play in ALS.

Many GWAS and family pedigree studies have failed to identify the 60% missing heritability.

How can we go further with genetics?

Mechanistic understanding – multi-omic perspective



Personalised medicine

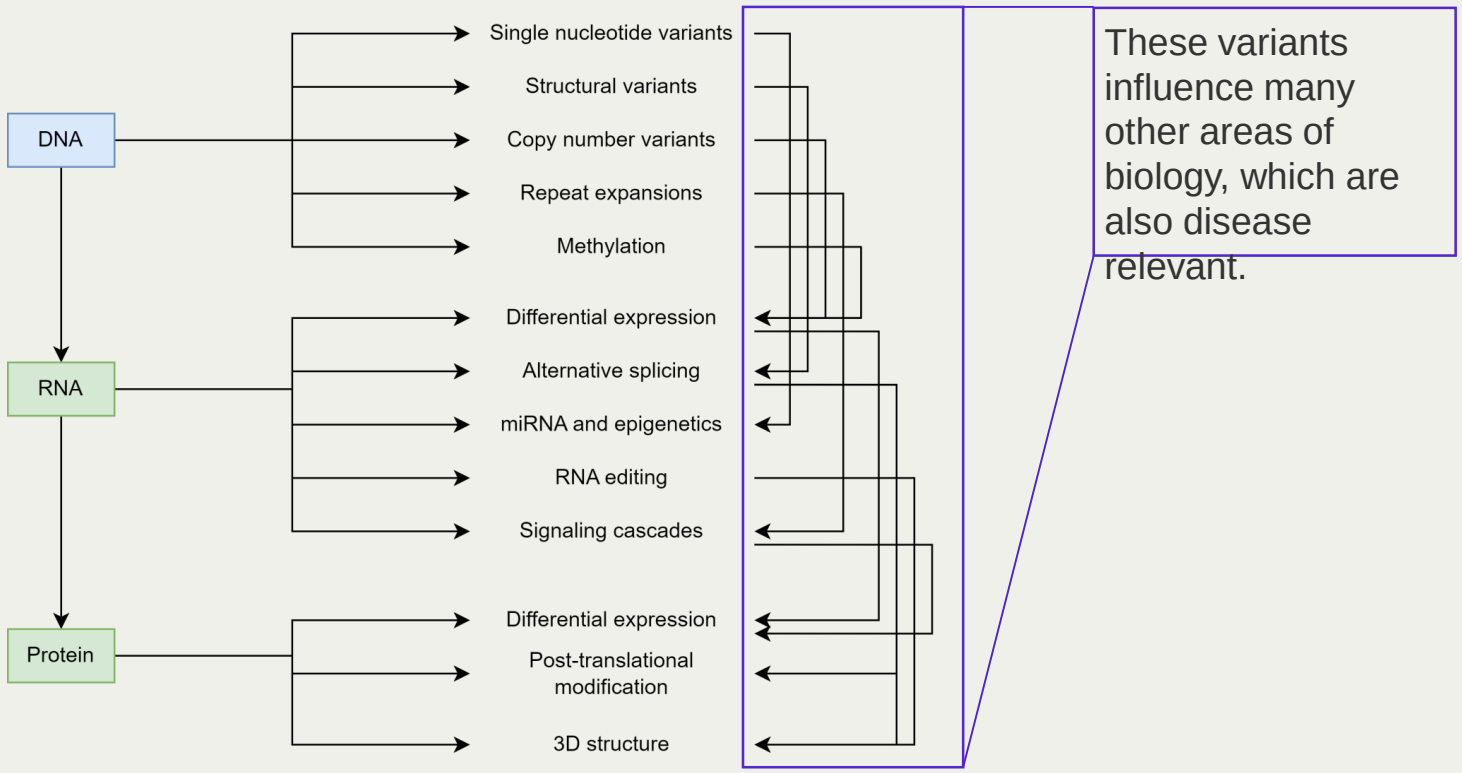
The difficulty in finding ALS causing variants in large population studies suggests that they are hard to discover.

We may need to take a personalised approach to discover disease driving genetic variants in ALS patients.

This will help us work out the disease mechanism and find new therapeutic targets.

How can we go further with genetics?

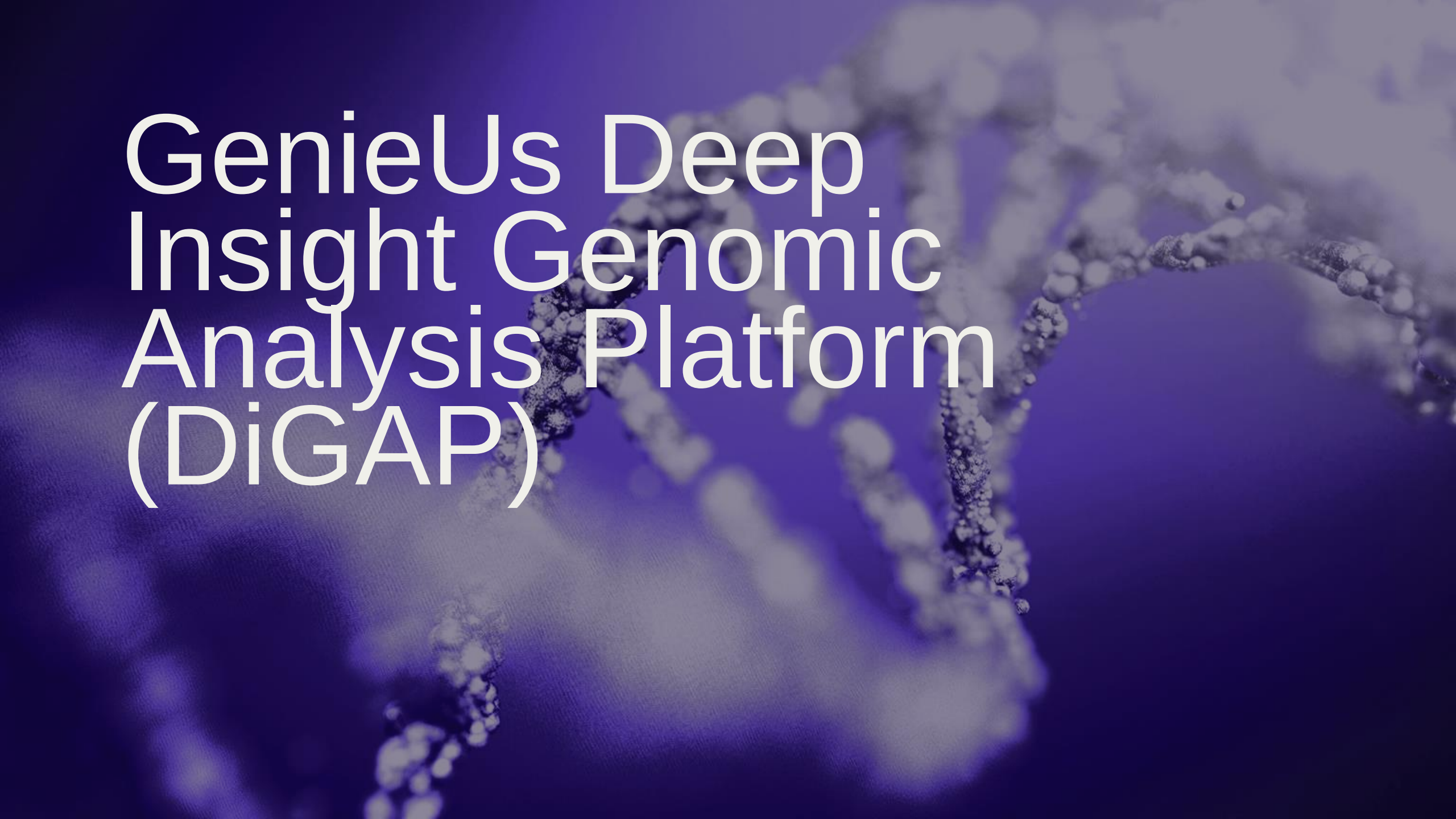
Mechanistic understanding – multi-omic perspective



Consequences

Understanding the flow on effects of genetic variants would also be a big help in describing disease processes for individual patients.

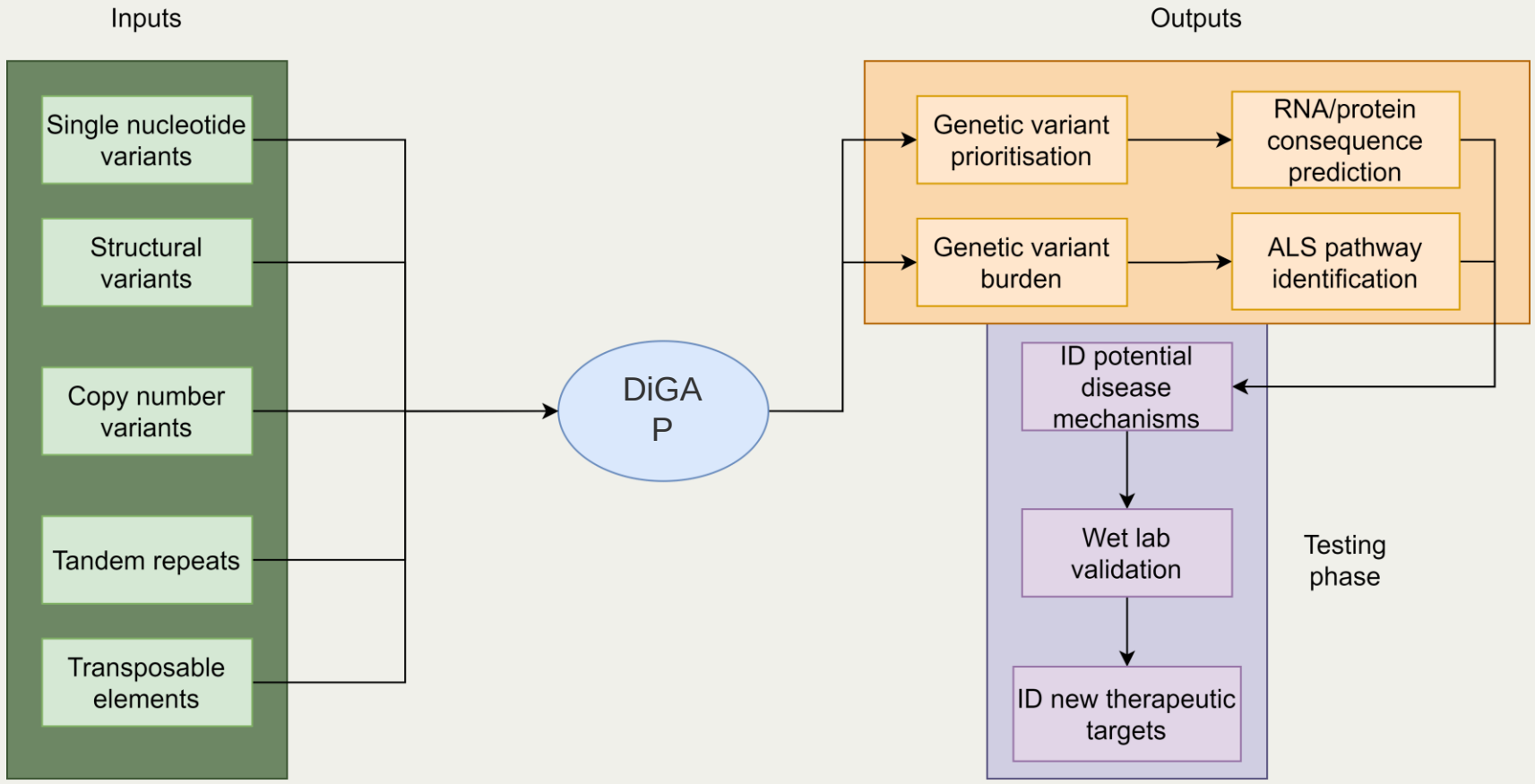
With this knowledge, we could **propose new therapies** or suggest existing therapies for ALS patients.


GenieUs Deep Insight Genomic Analysis Platform (DiGAP)

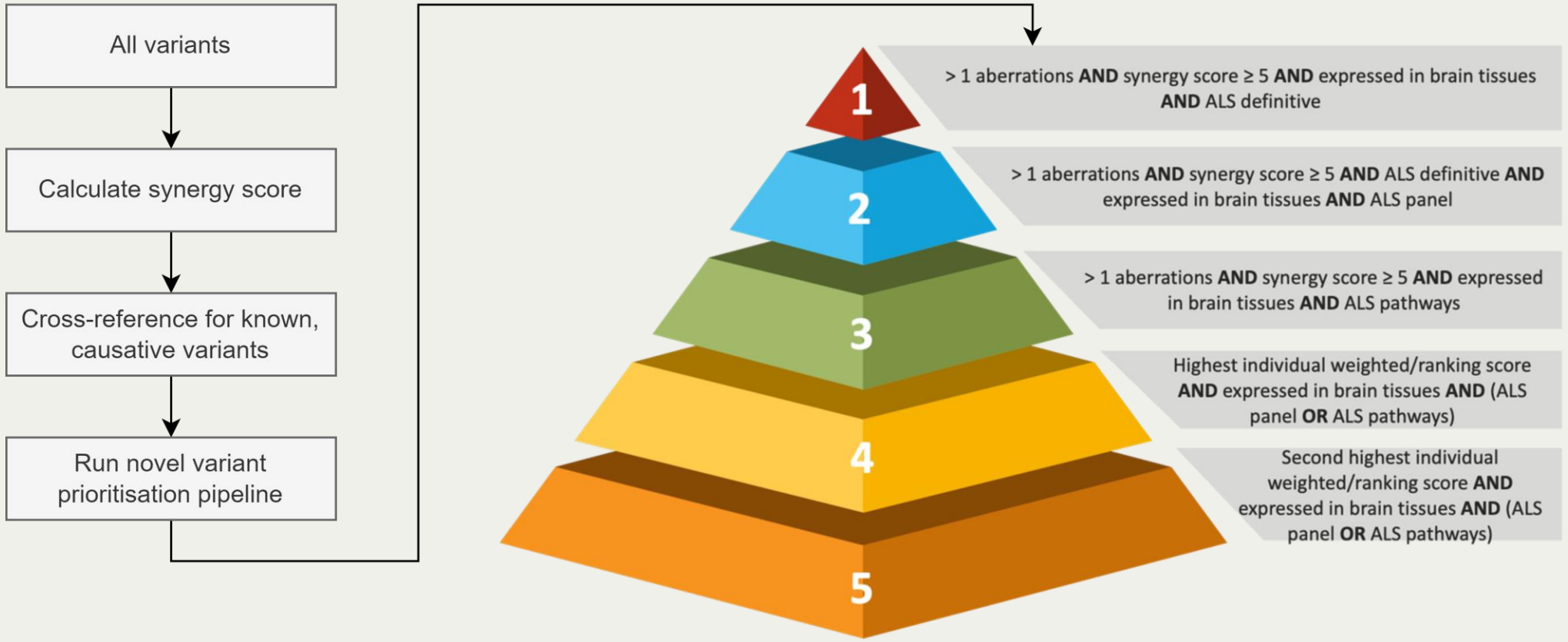
DiGAP Development

Towards an integrated understanding

We are currently developing DiGAP to be capable of integrating many types of genetic information to **guide us in our search for new biomarkers and therapeutics**.

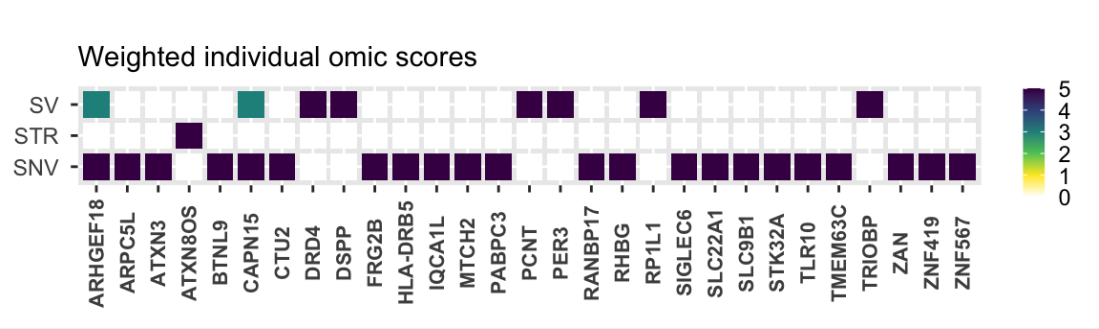


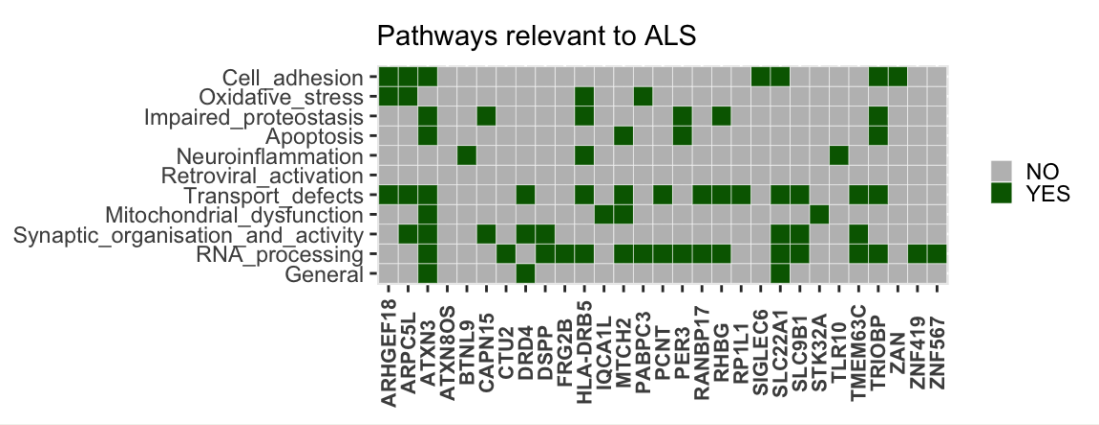
Variant prioritisation system



*patent pending

ALS pathways





Novel variants

With over 90% of sporadic ALS patients having no family history, we expect that we will need to identify novel genetic variants in many patients.

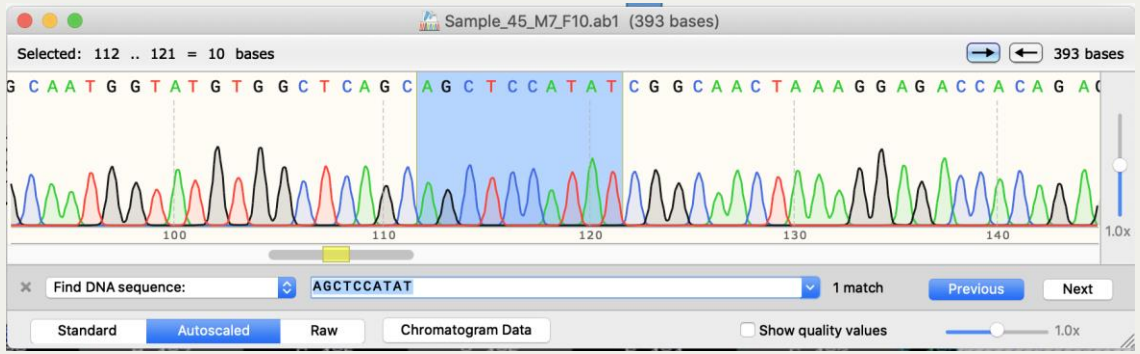
We have developed a variant prioritisation system that identifies extremely rare, predicted pathogenic variants in brain related genes.

*patent pending

Case study

Case study – *de novo* mutations

	WT	Heterozygous	Homozygous
PA_000000001 (507)		Y	
PA_000000002 (507)		Y	
PA_000000003 (507)		Y	
PA_000000004 (507)		Y	
PA_000000009 (Mother)	Y		
PA_000000012 (Father)	Y		
PA_000000014 (Brother)	Y		
PA_000000017 (Wife)	Y		

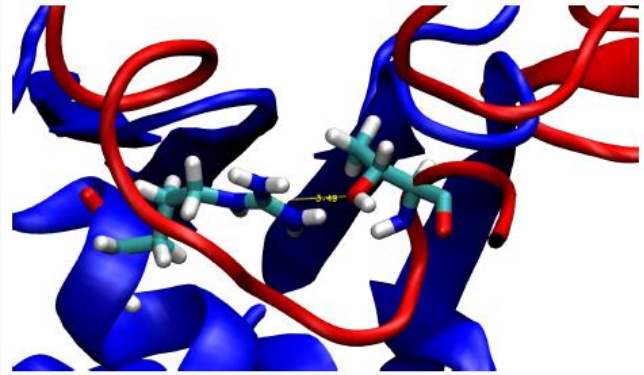


Interpretation comments: Phenotype overlap (Alzheimers disease - entrez), de novo het variant in proband, mostly damaging in silicos, not present in databases of non-ALS affected genomes, situated in protein domain regulatory subunit (dimer interaction - polypeptide binding site), present in helix secondary structure, highly conserved aa – likely pathological

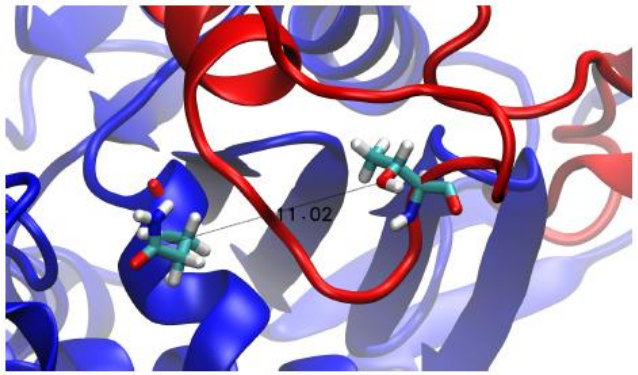
Validation: C>T mutation is present across 4 samples taken from the patient at different times according to Sanger sequenced PCR products

This is a true germline de novo mutation

Case study – *de novo* mutations



Wild type protein maintains close, stable interaction that excludes water molecules



Variant interaction allows water into this region of the molecule

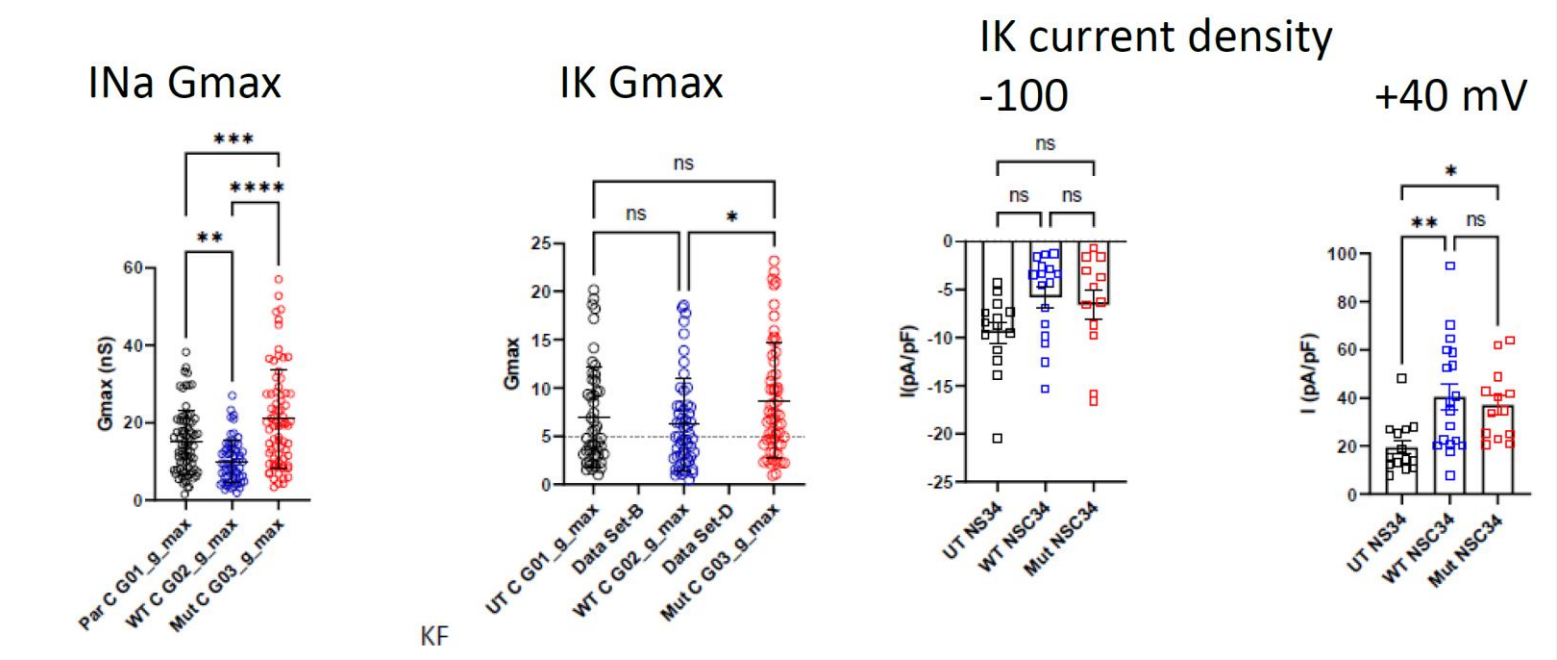
Molecular dynamics simulation

This mutation results in an amino acid substitution and changes the polarity at this critical residue.

This allows water molecules into a previously sealed binding pocket. The complex is not unstable because of this, but appears more labile.

This told us that this variant is likely to cause problems, so we modelled it in **a motor neuron cell line**.

Case study – *de novo* modelling

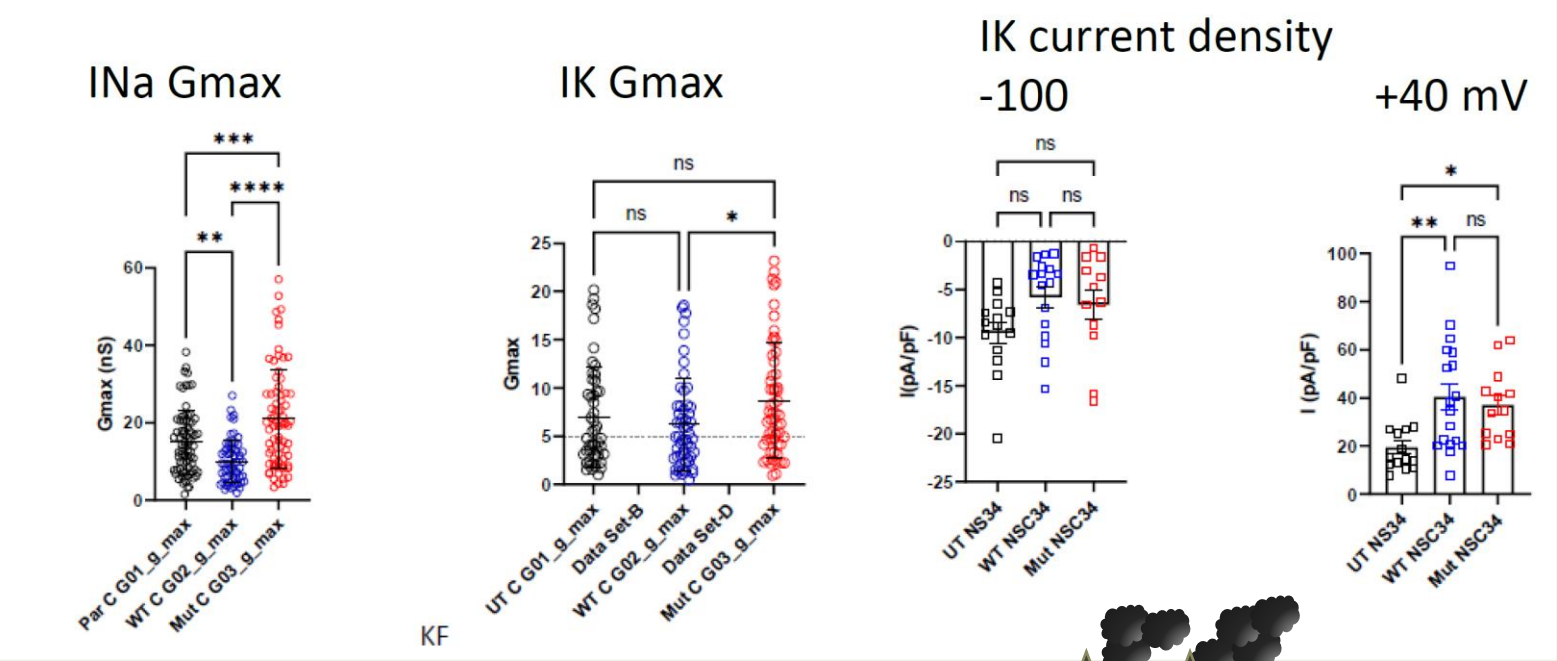


Electrophysiological modelling

The mutant cell line produces a larger Sodium current than the wild type or parental cell line, and a higher outward Sodium current.

This is **a hyperexcitable phenotype** that is now specifically associated with this variant. Hyperexcitability is an early and sustained feature in sporadic ALS patients.

Case study – *de novo* modelling



Electrophysiological modelling

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This is **a hyperexcitable phenotype** that is now specifically associated with this variant. Hyperexcitability is an early and sustained feature in sporadic ALS patients.

Next steps

Summary

New possibilities

Development strategies

We identified and characterised a unique genetic variant in an ALS patient.

The variant occurs in a gene not previously associated with ALS.

This variant drives hyperexcitability in a motor neuron model.

Next steps

Summary

New possibilities

Development strategies

Given that this variant is now tied to a specific phenotype, it can be considered as a therapeutic target.

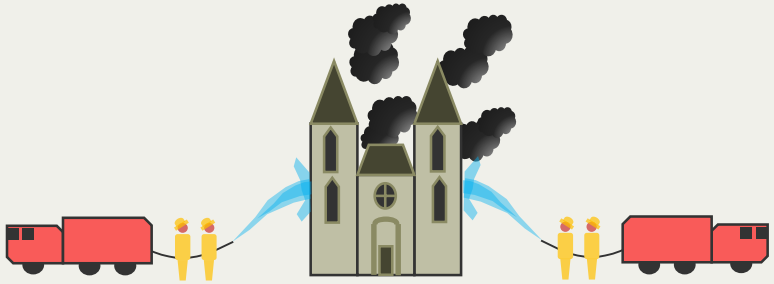
We are currently developing therapeutic strategies for this variant, based on this finding.

Next steps

Summary

New possibilities

Development strategies



- Drug screening to identify already safe/approved drugs that may act on this gene
- Development of new drugs to target this gene
- Supplementation with healthy RNA encoding our gene of interest
- Antisense oligonucleotide development to decrease the variant RNA levels, and increase the normal RNA levels

Thank you

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